ACTA ORTHOPAEDICA et TRAUMATOLOGICA TURCICA
www.aott.org.tr

Research Article

Vancomycin prophylaxis for revision hip arthroplasty in penicillin and cephalosporin sensitive patients: Is dose adjustment necessary in accordance with blood loss and fluid replacement?

Ömür Çağlar[1], Mehmet Kaymakoğlu[1], Akın Çil[2], Bülent Atilla[1], Fatma Sarıcaoğlu[3], Mazhar Tokgözoğlu[1]

[1]*Department of Orthopaedics and Traumatology, Hacettepe University, School of Medicine, Ankara, Turkey*
[2]*Department of Orthopaedics, University of Missouri-Kansas City, Missouri, USA*
[3]*Department of Anesthesiology, Hacettepe University, School of Medicine, Ankara, Turkey*

ARTICLE INFO

Article history:
Submitted January 8, 2020
Received in revised form
May 18, 2020
Last revision received
October 11, 2020
Accepted November 8, 2020

Keywords:
Vancomycin
Antibiotic prophylaxis
Periprosthetic infection
Revision arthroplasty

ORCID iDs of the authors:
Ö.Ç. 0000 0002 0346 8528;
M.K. 0000 0002 3548 5672;
A.Ç. 0000 0001 5916 0816;
B.A. 0000 0003 4796 0642;
F.S. 0000 0001 7307 2425;
M.T. 0000 0002 1375 8115.

ABSTRACT

Objective: The aims of this study were (1) to investigate the changes in the serum concentration of prophylactically administrated vancomycin in the perioperative period of revision hip arthroplasty in penicillin/cephalosporin-allergic patients, (2) to assess whether the postoperative re-administration of vancomycin is needed, and (3) to determine the relationships of vancomycin serum concentration with blood loss, body weight, and fluid replacement in such patients.

Methods: This study consisted of 29 patients (20 females, 9 males; mean age=63.3 years; age range=45-79 years) with a history of penicillin/cephalosporin allergy undergoing revision hip arthroplasty secondary to aseptic loosening or periprosthetic fractures. Serum vancomycin levels were measured (1) before administration of vancomycin, (2) at the time of skin incision, (3) every 1,5 hours thereafter until the end of the operation, (4) during the skin closure, and (5) after three and 12 hours from the initial dosage. Data regarding body weight, amounts of intraoperative blood loss, fluid and blood replacements and postoperative wound drainage were recorded.

Results: The average blood loss, fluid replacement, and drain volume were 1280.3±575.8 (500-2700) mL, 2922.6±768.8 (1700-4600) mL, and 480.2±163.7 (200-850) mL, respectively. The mean levels of serum vancomycin were 46.3±21.8 (14.1-80.7) mg/L at the time of skin incision, 17.9±4.7 (9.4-30.9) and 9.8±2.2 (4.3-13.8) mg/L after 1.5 and 3 hours from the beginning of the surgery and 5.1±1.1 (2.9-6.8)mg/L after 12th hour postoperatively. The measured vancomycin levels were below the effective serum concentrations (< 5 mg/L) for 18 patients at 12 hours the administration of the first dose. A moderate level negative correlation between the blood loss/body weight ratio and vancomycin levels was found (p=0.004, r=-0.493). Predictive ROC curve analysis resulted in determining a blood loss volume higher than 1150 ml and a blood loss/body weight ratio higher than 18,5 is significant to estimate the vancomycin level below the minimum effective serum level at 12th hour postoperatively (AUC=0.793±0.16, p=0.009, AUC=0.753) 26±0.12, p=0.025, respectively).

Conclusion: Evidence from this study has indicated vancomycin concentration at 12th hour is below the effective level in most patients. Thus, earlier repetitive infusion of vancomycin seems to be necessary in penicillin/cephalosporin-allergic patients undergoing revision hip arthroplasty, especially in those with high blood loss.

Level of Evidence: Level III, Therapeutic Study

Introduction

Despite improvements in implant technology and a better understanding of the reasons for total hip arthroplasty (THA) failure, revision THA remains a burden in orthopedic practice. Periprosthetic joint infection (PJI) is one of the leading causes of THA revision with prolonged hospitalization and high medical costs (1). Overall, PJI occurs in 0.6%-2% of THA surgeries performed worldwide, and PJI consists of nearly 14% of all revision cases (2-4). The infection rates after revision cases due to aseptic loosening, periprosthetic fractures, or dislocations are even higher than those of primary THA operations (5).

Antibiotic prophylaxis is a keystone for preventing PJI. A strong consensus for the use of vancomycin prophylaxis in patients with hypersensitivity to penicillin/cephalosporins or in orthopedic centers with high rates of MRSA was described by the 2nd International Consensus Meeting on Musculoskeletal Infection in 2018 (6). It is well known that due to the short elimination time of most penicillin/cephalosporin group antibiotics, repetitive intraoperative dosages are needed, especially in long-lasting cases such as revision surgeries.

Vancomycin has a relatively short (3-6 h) elimination time in patients with normal kidney function, similar to penicillin/cephalosporin group antibiotics (7). Thus, the minimum effective serum level may not be maintained with a single prophylactic dosage in long-lasting surgeries or in the presence of excessive blood loss, using theoretically similar penicillin/cephalosporin group antibiotics (8). Despite general suggestions from the literature about prophylactic antibiotics, there are no studies that show how the serum concentration of vancomycin changes after major orthopedic procedures with major blood loss and excessive fluid replacement until the repeat dose 12

Corresponding Author:
Ömür Çağlar
omurcaglar@hotmail.com

Cite this article as: *Çağlar Ö, Kaymakoğlu M, Çil A, Atilla B, Sarıcaoğlu F, Tokgözoğlu M. Vancomycin prophylaxis for revision hip arthroplasty in penicillin and cephalosporin sensitive patients: Is dose adjustment necessary in accordance with blood loss and fluid replacement? Acta Orthop Traumatol Turc 2021; 55(1): 53-6.*

DOI: 10.5152/j.aott.2021.20019

h later. We investigated changes in the serum concentration of prophylactically administered vancomycin, the need for postoperative re-administration, and its relationship with blood loss, body weight, and fluid replacement, in patients who underwent revision hip arthroplasty.

Materials and Methods

After ethics committee approval from our institution, we prospectively evaluated 29 patients (20 women, 9 men) who underwent revision hip arthroplasty due to aseptic loosening or periprosthetic fracture between 2007 and 2012. All patients had a history of allergic symptoms to penicillin/cephalosporin group antibiotics. Patients who were known to be allergic to glycopeptides; had denied giving informed consent; had preoperative elevated liver function (AST > 40 U/L, ALT > 45 U/L) or renal function tests (GFR<60, creatinine > 1.2) that indicated hepatorenal dysfunction; were thought to have clinical signs (tenderness, increase of temperature, edema, redness); had laboratory (elevated ESR > 25 mm/h, CRP > 0.8 mg/mL) or histological (frozen section) signs of infected arthroplasty; and/or had tissue culture positive were excluded from the study. The prophylactic vancomycin dose was weight-based, and a dose of 15 mg/kg in 100 mL of saline was intravenously infused over 60 minutes before the skin incision (9). The minimum effective serum vancomycin level was determined to be 5 mg/L (10, 11). Serum vancomycin levels were measured via blood taken in the following order: 1. Before administration of vancomycin, 2. At the time of skin incision, 3. Every 1, 5 h thereafter until the end of the operation, 4. During skin closure, and 5, 3 and 12 h after the initial dosage. The intraoperative blood loss, fluid and blood replacements, and postoperative wound drainage were measured and recorded. Intraoperative blood loss was determined as the blood volume aspirated from the surgical site and the number of fully blood loaded sponges (10-20 mL per sponge). Surgery times and body weights of the patients were noted.

Statistical analysis

Mann-Whitney U test and ROC curve regression analysis were used to analyze the relationship between postoperative vancomycin levels and blood loss. Pearson's correlation test was used to determine the correlation between vancomycin and blood loss/body weight ratio. IBM Statistical Package for Social Sciences version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis.

Results

The mean age of the 29 patients was 63.3±9.6 (45-79) years. The average intraoperative blood loss, fluid replacement, and drain volume were 1280.3±575.8 (500-2700) mL, 2922.6±768.8 (1700-4600) mL, and 480.2±163.7 (200-850) mL, respectively. The mean serum vancomycin levels were 46.3±21.8 (14.1-80.7) mg/L at the time of skin incision, 17.9±4.7 (9.4-30.9) and 9.8±2.2 (4.3-13.8) mg/L after 1.5 and 3 h from the beginning of the surgery and 5.1±1.1 (2.9-6.8) mg/L after 12 h postoperatively (Figure 1). All patients had higher serum vancomycin concentrations than the minimum effective serum level until 3 h after the beginning of the surgery. However, we observed concentrations lower than the minimum effective serum level (< 5 mg/L) in 18 patients (62.1%) at 12 h postoperatively (mean: 4.0±0.6). The remaining 11 patients had higher vancomycin levels (> 5 mg/L) (mean: 5.8±0.6). The blood loss and body weight data of all patients are listed in Table 1. We found a statistical difference in intraoperative blood loss between patients with low and high vancomycin concentrations at 12 h (p=0.008) and a moderate negative correlation between the blood loss/body weight ratio and vancomycin levels (p=0.004, r=- 0.493). There was also a statistically significant difference between the blood loss/body weight ratios of patients with low and high vancomycin concentrations (19.6±7.2 vs. 13.5±4.0, respectively, p=0.016). Predictive

Table 1. Ratio of blood losses and body weights of all patients and Vancomycin levels at 12th hour

Patient No.	Blood Loss (mL)	Body Weight (kg)	Blood Loss / Body Weight	12th Hour Vancomycin Level (mg/L)
1	2700	85	31	2,85
2	1700	65	26	3,03
3	900	63	14	3,39
4	800	58	13	3,53
5	1500	74	20	3,57
6	1400	79	17	3,61
7	1300	67	19	3,81
8	2500	85	29	3,86
9	2300	82	28	3,91
10	900	66	13	3,91
11	1800	80	22	4,19
12	1300	60	21	4,39
13	700	68	10	4,55
14	950	69	13	4,57
15	1300	77	16	4,63
16	1280	62	20	4,79
17	800	84	9	4,91
18	2400	73	32	4,97
19	1350	77	17	5,08
20	1000	69	14	5,11
21	1400	80	17	5,28
22	1300	65	20	5,40
23	650	63	10	5,61
24	750	72	10	5,79
25	700	55	12	5,79
26	1200	64	18	6,04
27	500	64	7	6,41
28	800	70	11	6,57
29	900	65	13	6,96

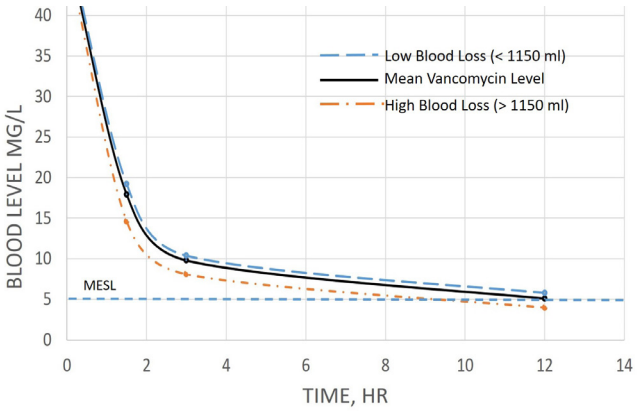

Figure 1. Time-dependent mean vancomycin concentrations
MESL: Minimum effective serum level

HIGHLIGHTS

- Redosage time of prophylactically administered vancomycin in case of excessive blood loss or prolonged major orthopedic operations is controversial.
- Weight-based administration of vancomycin must be considered for all patients.
- According to our findings, we practically suggest that repetative dosage of vancomycin at 12 h should be made 2-3 hours earlier in patients with >1150 mL blood loss and >18.5 blood loss/body weight ratio to maintain minimum effective serum level of vancomycin.

Table 2. Comparisons of blood losses, fluid replacements, drain volumes and surgery times between two different vancomycin blood level groups

Blood Level at 12th hour (mg/L)	Number of patients	Mean Intraoperative Blood Loss (mL)*	Mean Adm. Fluid (mL)**	Mean Drainage (mL)	Surgery Time (min)
< 5 mg/L	18	1476	3050	492	148.9
> 5 mg/L	11	959	2840	470	131.7
Overall mean	29	1280	2923	480	142.4

*p<0.05, **includes fluid and blood replacements until 12th hour postoperatively, Adm: Administered

ROC curve analysis revealed that blood loss volume greater than 1150 mL, and blood loss/body weight ratio more than 18.5 was significant for estimating vancomycin levels below the minimum effective serum level at 12 h postoperatively (AUC=0.793±0.16, p=0.009, AUC=0.753 ± 0.12, p=0.025, respectively).

The surgery times of the patients with a lower vancomycin concentration than the minimum effective serum level were longer than those of patients with a higher vancomycin concentration (148.9±23.2 vs. 131.7±18.5 minutes, respectively, p=0.15); however, the difference was not statistically significant. Other variables between the groups (fluid replacement and drain volume) were also not statistically significant (p>0.05) (Table 2).

Discussion

PJI remains a major cause of THA revision. An analysis of the major causes of THA revisions in the USA showed that the ratio of PJI-related revisions remained constant between 2007 and 2013. The number of patients who suffered from PJI increased 23%, indicating that more primary THA operations are being performed (3). Therefore, appropriate antibiotic prophylaxis is important for avoiding the economic and psychological burden of PJI-related THA revisions. This is the first study to report the inadequacy of routine vancomycin prophylaxis until administration of the repetitive dose 12 h after the initial administration in major orthopedic procedures with high blood loss.

Vancomycin is a routinely used prophylactic antibiotic for patients who have a history of allergic reactions to penicillin/cephalosporin group antibiotics and during major surgical procedures at institutions with a high rate of infections caused by MRSA, or even for local prophylaxis in some orthopedic interventions (6, 12, 13). Despite the previous reports that a single dose of vancomycin was sufficient for effective therapeutic levels up to 20 h in total knee arthroplasty patients, the routine redosing period of vancomycin is 12 h postoperatively (14). According to the 2017 Guidelines for the Prevention of Surgical Site Infection published by the Centers for Disease Control and Prevention (CDC), redosing of antimicrobial prophylaxis with penicillin/cephalosporin group antibiotics is recommended if the surgery lasts more than 3-4 h or a major blood loss exists (9). Although Meter et al. did not suggest re-administration of cephazolin in less than 4-h intervals, even with a blood loss of 2000 mL in THA patients, other authors such as Swoboda et al. have suggested a redosing before the planned redosing time if there is more than 1500 mL of blood loss in a study performed with 11 patients who underwent spinal instrumentation (8, 15).

Our results revealed that routine antibiotic prophylaxis with vancomycin in major orthopedic procedures requires a more serious approach. Resistant strains (e.g., MRSA) can rapidly grow in environments with an inadequate dosing of antibiotic prophylaxis (16). In order to prevent underdosage, Catanzano et al. pointed out that weight-related dose adjustment is necessary in vancomycin prophylaxis and patient-related factors (such as weight, age, and sex) should be considered when determining adequate dosage (17). In a retrospective study by Kheir et al., adequately dosed patients with vancomycin did not develop PJI with MRSA in contrast to higher rates of PJI in underdosed patients. They also found that 64% of the patients in the study group were underdosed due to inadequate dosing without weight-based dose adjustment (18). According to our results, even with weight-based dose adjustment, the minimum effective serum level might not be maintained until the next routine dose of vancomycin prophylaxis in major orthopedic procedures with high blood loss. More than half of the patients in our study (18 patients, 62.1%) were below the minimum effective serum level at 12 h postoperatively. A negative correlation was found between vancomycin levels and blood loss/body weight ratio, indicating that, along with blood loss volume alone, a greater blood loss per kg is meaningful. Considering these two parameters, we suggest more caution in patients with high volume of blood loss (>1150 mL) and high blood loss/body weight ratio (>18.5). The surgery times of the patients with lower concentration than the minimum effective serum level at 12 h were higher than those of the patients with higher concentrations (148.9±23.2 vs. 131.7±18.5 min); however, the difference was not statistically different. We think that this insignificant difference was due to the small number of patients in our study, but suggest caution about the vancomycin levels in patients with longer operation durations.

Drainage volumes and administered fluid volumes were nearly equal in both groups. We did not consider those factors when comparing the two groups. However, fluid administration in postoperative patients is important for both vital functions and pharmacodynamics. Insufficient fluid therapy can result in diminished renal function and reduce the clearance of vancomycin and increase its serum levels and nephrotoxicity. Conversely, excessive fluid therapy can result in decreased antibiotic concentration and hypervolemia. To avoid acid-base disturbance, Ringer's lactate, normal saline solutions, and erythrocyte suspensions were used together during intra- and postoperative patient care (19-21).

We did not observe any adverse effects of vancomycin, such as nephrotoxicity or allergic reactions, in any of our patients in the short-term follow-up. One of the main limitations of our study was the absence of long-term follow-up. However, our main goal was to evaluate serum vancomycin levels postoperatively. We also did not assess whether any patient experienced PJI in the long term, especially those with low serum vancomycin levels.

In this study, we wanted to draw attention to the possible insufficiency of prophylactic vancomycin dosage in penicillin/cephalosporin-sensitive revision hip arthroplasty patients with high blood loss or high blood loss/body weight ratio. Even after a weight-based administration of vancomycin prophylaxis, adequate serum levels may not be maintained prior to the succeeding dose 12 h postoperatively. As such, we suggest obtaining serum levels of vancomycin to determine earlier repetitive dose requirements in all major orthopedic procedures with high blood loss or blood loss/body weight ratio.

Ethics Committee Approval: Ethics committee approval was received for this study from the Committee of Hacettepe University. (Protocol No: B.30.2.HAC.0.01.00.05/1102 - 28.10.2005)

Informed Consent: Patients who were known to be allergic to glycopeptides; had denied giving informed consent.

Author Contributions: Concept - M.T.; Design - B.A., Ö.Ç., A.Ç.; Supervision - B.A., M.T., A.Ç.; Data Collection and/or Processing - Ö.Ç., F.S.; Analysis and/or Interpreta-

tion - Ö.Ç.; Literature Review - M.K., F.S.; Writing - M.K., Ö.Ç.; Critical Review - M.T., F.S., A.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Alp E, Cevahir F, Ersoy S, Güney A. Incidence and economic burden of prosthetic joint infections in a university hospital: A report from a middle-income country. J Infect Public Health 2016; 9: 494-8. [Crossref]
2. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014; 27: 302-45. [Crossref]
3. Rajaee SS, Campbell JC, Mirocha J, Paiement GD. Increasing burden of total hip arthroplasty revisions in patients between 45 and 64 years of age. J Bone Joint Surg Am 2018; 100: 449-58. [Crossref]
4. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic joint infection risk after total hip arthroplasty in the Medicare population. J Arthroplasty 2009; 24(6 Suppl): 105-9. [Crossref]
5. Bohl DD, Samuel AM, Basques BA, Della Valle CJ, Levine BR, Grauer JN. How much do adverse event rates differ between primary and revision total joint arthroplasty? J Arthroplasty 2016; 31: 596-602. [Crossref]
6. Schwarz EM, Parvizi J, Gehrke T, et al. 2018 International Consensus Meeting on Musculoskeletal Infection: Research Priorities from the General Assembly Questions. J Orthop Res 2019; 37: 997-1006. [Crossref]
7. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009; 66: 82-98. [Crossref]
8. Meter JJ, Polly DW Jr, Brueckner RP, Tenuta JJ, Asplund L, Hopkinson WJ. Effect of intraoperative blood loss on the serum level of cefazolin in patients managed with total hip arthroplasty. A prospective, controlled study. J Bone Joint Surg Am 1996; 78: 1201-5. [Crossref]
9. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg 2017; 152: 784-91. [Crossref]
10. Larsson AJ, Walker KJ, Raddatz JK, Rotschafer JC. The concentration-independent effect of monoexponential and biexponential decay in vancomycin concentrations on the killing of Staphylococcus aureus under aerobic and anaerobic conditions. J Antimicrob Chemother 1996; 38: 589-97. [Crossref]
11. James CW, Gurk-Turner C. Recommendations for monitoring serum vancomycin concentrations. Proc (Bayl Univ Med Cent) 2001; 14: 189-90. [Crossref]
12. Eren B, Karagöz Güzey F, Kitiş S, Özkan N, Korkut C. The effectiveness of pedicle screw immersion in vancomycin and ceftriaxone solution for the prevention of postoperative spinal infection: A prospective comparative study. Acta Orthop Traumatol Turc 2018; 52: 289-93. [Crossref]
13. Theologis AA, Demirkıran G, Callahan M, Pekmezci M, Ames C, Deviren V. Local intrawound vancomycin powder decreases the risk of surgical site infections in complex adult deformity reconstruction: A cost analysis. Spine 2014; 39: 1875-80. [Crossref]
14. Eshkenazi AU, Garti A, Tamir L, Hendel D. Serum and synovial vancomycin concentrations following prophylactic administration in knee arthroplasty. Am J Knee Surg 2001; 14: 221-3.
15. Swoboda SM, Merz C, Kostuik J, Trentler B, Lipsett PA. Does intraoperative blood loss affect antibiotic serum and tissue concentrations? Arch Surg 1996; 131: 1165-71; discussion 71-2. [Crossref]
16. O'Brien TF. Emergence, spread, and environmental effect of antimicrobial resistance: how use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. Clin Infect Dis 2002; 34 Suppl 3: S78-84. [Crossref]
17. Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J, 3rd. The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. Iowa Orthop J 2014; 34: 111-7.
18. Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: Incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. Clin Orthop Relat Res 2017; 475: 1767-74. [Crossref]
19. Kim YW. Antimicrobial-induced Electrolyte and Acid-Base Disturbances. Electrolyte Blood Press 2007; 5: 111-5. [Crossref]
20. Bernier SP, Surette MG. Concentration-dependent activity of antibiotics in natural environments. Front Microbiol 2013; 4: 20. [Crossref]
21. Zelenitsky SA, Ariano RE, Harding GKM, Silverman RE. Antibiotic pharmacodynamics in surgical prophylaxis: An association between intraoperative antibiotic concentrations and efficacy. Antimicrob Agents Chemother 2002; 46: 3026-30. [Crossref]